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TITLE: Extended Storage of Pathogen-Reduced Platelet Concentrates (PRECON)

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14. ABSTRACT This grant pertains to finding novel approaches for storage of platelets for transfusion. Our project proposes to determine the efficacy of using a pathogen inactivation technique (Mirasol) coupled with a platelet additive solution (PAS) to extend the life of stored platelets. Our project also aims to determine how long acceptable platelet viability can be maintained in platelets stored at 4°C.					
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Extended Storage of Pathogen-Reduced Platelet Concentrates (PRECON)

Grant Number 13335012

Annual Report

26-SEP-2015 to 25-SEP-2016

Table of Contents

1. Introduction	7
2. Keywords	7
3. Overall Project Summary	7
4. Key Research Accomplishments.....	8
5. Conclusion	8
6. Publications, Abstracts, and Presentations	10
7. Inventions, Patents and Licenses	10
8. Reportable Outcomes	10
9. Other Achievements	10
10. References.....	10
11. Appendices	10
• Statement of Work - Extended Storage of Pathogen-Reduced Platelet Concentrates	11
• Protocol - Cold Apheresis Platelets in Isoplate (CAPI)	13
• Quad Chart	27

Extended Storage of Pathogen-Reduced Platelet Concentrates (PRECON)
(Previously Pathogen-Reduced, Plasmalyte-Extended Stored Platelets)
Grant Number 13335012
Annual Report
26-SEP-2015 to 25-SEP-2016

INTRODUCTION: The purpose of this project is to find better ways to store platelets for patients that need platelet transfusions. A deeper mechanistic understanding of the effects of collection and storage on platelet function could greatly aid in improving the availability and efficacy of platelets both on the battlefield and in the civilian transfusion setting. In this research study, we are interested in evaluating the novel combinations of collection, storage and pathogen reduction approaches on the structural and functional properties of platelets and on platelet viability and function following transfusion.

KEY WORDS: 4°C storage, bleeding, cold storage, extended storage, hemorrhage, hemostasis, Isoplate, InterSol, pathogen inactivation, pathogen reduction, pathogen reduction technology, PRT, platelet additive solution, PAS, platelet recovery and survival, platelet storage, platelet storage solution, platelets, refrigerated storage, thrombocytopenia, transfusion, whole blood

OVERALL PROJECT SUMMARY: The following specific aims were described in the original statement of work, Extended Storage of Pathogen-Reduced Platelet Concentrates (PRECON).

1. Determine the optimum conditions for extended storage of autologous platelet concentrates in a platelet additive solution (PAS).
2. Evaluate the effects of Mirasol treatment of autologous whole blood (WB) on extended storage of PAS-stored platelet concentrates prepared from treated WB.
3. Determine the post-transfusion recovery and survival of pre-storage pooled extended stored platelet concentrates prepared from Mirasol-treated WB given to thrombocytopenic patients.

An evaluation of changes in the structural and functional properties of platelets stored as whole blood under refrigeration [Assessment of Whole Blood Cold Stored Platelets (Brrr Study)] has been completed. Results of this trial were submitted in a document entitled, 'Final Report - Storage of Platelets in Whole Blood at 4°C,' that was included in last year's annual report.

We are currently evaluating apheresis platelets stored at 4°C either in a platelet additive solution, such as InterSol or Isoplate, or stored in plasma. The protocol, entitled Cold Apheresis Platelets in Isoplate (CAPI), is attached. Briefly, an apheresis platelet unit is collected from a healthy subject and divided into two units. One half of the split unit is stored in plasma at 4°C for 3 days (control), the other half is stored in a PAS/plasma mixture or in plasma alone (test). The test unit is stored at 4°C for 10 days. Subjects receive radiolabeled platelet infusions on Day 3 and Day 10 to evaluate platelet recovery and survival. Each subject's platelet recovery and survival is considered acceptable if they are ≤40% less than the subject's corresponding 3-day stored sample measurements. Storage periods will be increased from 10 days in 2 day increments after 5 units pass acceptance criteria. In addition to the in vivo platelet

recovery and survival assays a number in vitro metabolic and functional platelet assays are performed on Day 3 and at the end of storage.

KEY RESEARCH ACCOMPLISHMENTS:

- Completion of study of platelets stored as whole blood at 4°C (Brrr Study)
- Publication in *Blood* – results of study of platelets stored as whole blood at 4°C
- Initiation of study of apheresis platelets stored 4°C in different additive solutions and in plasma alone (CAPI Study)

CONCLUSION:

Brrr Study

Our study of platelets stored as whole blood at 4°C demonstrated that end-over-end rotation is required to reduce platelet adherence to the walls of the bag. Platelet yields in whole blood post-storage average 7.0 to 9.2 x 10¹⁰. Thus, the FDA requirement of 5.5 x 10¹⁰ platelets/concentrate are easily met. At storage times between 10 to 15 days stored recoveries average 50% of fresh recoveries, stored survivals average >1 day, proposed post-storage criteria for whole 4°C stored platelets are met and based on in vitro measurements, the platelets are highly activated.

CAPI study

Table 1, on the following page, gives the results of the radiolabeled autologous platelet recovery and survival data for our currently-completed studies. The control platelets were all stored in plasma for 3 days as this is the longest FDA approved storage time for platelets stored at 4°C. For the 3-day platelets, average recoveries were 41 ± 10% (1 S.D.) and survivals 1.9 ± 0.6 days (n=9). These data are consistent with prior data on recoveries and survivals of platelet concentrates stored in plasma at 4°C for 3 days.

Our plan is to store the other half of each donor's apheresis platelets in 65% Intersol/35% plasma, 65% Isoplate/35% plasma, and 100% plasma for 10 days at 4°C. A total of 5 donors will be stored under each condition, the data will be evaluated and a decision will be made in consultation with USAMDA about how we should proceed. Although the numbers are still small, it appears that Intersol gives much better post-storage viability than platelets stored in Isoplate. Interestingly, plasma-only storage may give better results than storage in either of the two storage solutions tested. There is now interest in using TPAS as a storage solution for platelets, and we have asked Terumo to send us TPAS to test after they receive IND approval to store platelets in TPAS.

As opposed to platelets stored in the two storage solutions, the number of platelets recovered after platelets are stored in plasma are about 25% less than the platelet count pre-storage. In our whole blood 4°C platelet storage study, we found that platelets adhered to the walls of the bag, and yield was markedly improved by agitating the whole blood during storage.

TABLE 1
CAPI *IN VIVO* TESTING

Subject Study ID	3 Day Recovery in Plasma (%)	10 Day Stored Recovery in Intersol (%) [*]	10 Day Stored Intersol Recovery as a % of 3 Day Recovery in Plasma	3 Day Survival in Plasma (Days)	10 Day Stored Survival in Intersol (Days)	10 Day Stored Intersol Survival as a % of 3 Day Survival in Plasma
CA620	57	24	42	2.3	1.5	64
CA622	44	20	44	2.0	1.0	49
CA623	39	18	47	2.1	1.0	48
CA624	27	13	49	1.1	0.7	59
Average ±1 SD	42 ± 12	19 ± 5	46 ± 3	1.9 ± 0.5	1.1 ± 0.3	55 ± 8

Subject Study ID	3 Day Recovery in Plasma (%)	10 Day Stored Recovery in Isoplate (%) ^{**}	10 Day Stored Isoplate Recovery as a % of 3 Day Recovery in Plasma	3 Day Survival in Plasma (Days)	10 Day Stored Survival in Isoplate (Days)	10 Day Stored Isoplate Survival as a % of 3 Day Survival in Plasma
CA630	31	6	18	1.7	1.1	62
CA628	52	7	14	0.8	0 ^{***}	NA
CA635	34	10	30	2.0	1.6	80
Average ±1 SD	39 ± 11	8 ± 2	21 ± 8	1.5 ± 0.6	1.4 ± 0.4	71 ± 13

Subject Study ID	3 Day Recovery in Plasma (%)	10 Day Stored Recovery in Plasma (%)	10 Day Stored Plasma Recovery as a % of 3 Day Recovery in Plasma	3 Day Survival in Plasma (Days)	10 Day Stored Survival in Plasma (Days)	10 Day Stored Plasma Survival as a % of 3 Day Survival in Plasma
CA639	40	26	65	2.7	1.5	58
CA641	42	27	64	2.0	1.5	74
Average ±1 SD	41 ± 1	27 ± 1	65 ± 0.7	2.4 ± 0.5	1.5 ± 0	66 ± 11

NA – Not applicable.

* Platelets stored in 65% Intersol and 35% plasma.

** Platelets stored in 65% Isoplate and 35% plasma.

*** Ten day stored radioactive counts too low to calculate a survival. After initial 1 hour post infusion sample, radioactivity was at background level.

We plan to evaluate the impact of platelet agitation in cold storage and to change our comparator (control) to fresh platelets in the next reporting period.

A deeper understanding of the effects of cold storage on platelet function could greatly aid in improving the availability of platelets on the battlefield and in the civilian transfusion setting.

PUBLICATIONS, ABSTRACTS, and PRESENTATIONS: Slichter SJ, Fitzpatrick L, Jones MK, Pellham E, Bailey SL, Gettinger I. In vivo viability of platelets stored in whole blood at 4C. (Abstract) Blood 2015;126:2338.

INVENTIONS, PATENTS AND LICENSES: Nothing to report.

REPORTABLE OUTCOMES: Nothing to report.

OTHER ACHIEVEMENTS: Nothing to report.

REFERENCES: None

APPENDICES:

- Statement of Work - Extended Storage of Pathogen-Reduced Platelet Concentrates (PRECON) dated 7/21/14
- Protocol - Cold Apheresis Platelets in Isoplate (CAPI)
- Quad Chart

Date: 07-21-2014

Project Title: Extended Storage of Pathogen-Reduced Platelet Concentrates (PRECON)

Project Contract: W81XWH-13-2-0089

Effective date: 26SEP2013

PI: Sherrill J. Slichter, MD

STATEMENT OF WORK:

Specific Aims/Study Design:

Whole blood (WB) will be held for 22 ± 2 hours at 22°C before preparing a platelet (plt) concentrate for all aims. For Specific Aims 1 and 2, up to 12 normal subjects will be evaluated for each storage condition using autologous radiolabeled stored *versus* fresh plt recovery and survival measurements to identify the best Platelet Additive Solution (PAS) storage conditions that meet FDA post-storage plt viability criteria.

For all Specific Aims, we will need both local IRB and HRPO approvals. For Specific Aims 2 and 3, an IDE will be needed to permit Mirasol treatment of WB, and this IDE will be submitted by Terumo BCT.

Specific Aim 1: Determine the optimum conditions for extended storage of autologous plt concentrates in PAS.

Subjects (#)	Timeline (Weeks)
162	104

- 1a) Identify an acceptable storage bag.

Plt concentrates can be stored for 6 days in either plasma or 65% PAS/35% plasma in our standard Terumo plt storage bag (PVC plastic). However, Haemonetics apheresis plts can be stored for 13 days in Haemonetics bags (CLX plastic).

Plt concentrates will first be stored for 6 days in 65% PAS/35% plasma using our standard Terumo plt storage bag (PVC plastic). If FDA criteria are met, we will progressively increase the storage times in 1-day increments until the criteria are not met. If the FDA criteria are met for ≥ 9 days of storage, we will go to Aim 1b. If ≥ 9 day storage is not achieved, we will utilize the Pall CLX HP (high permeability) plt concentrate storage bags that should be similar to the Haemonetics CLX apheresis bag. We will repeat the same testing sequence with the Pall CLX bag as with the Terumo bag described above. If ≥ 9 day storage is not achieved, we will seal off the bottom half of a 1000 ml Fenwal polyolefin bag (PL2410) to reproduce the 500 ml volume of a plt concentrate storage bag. In prior studies using PAS, we have demonstrated that this bag gives the same apheresis 13-day storage results as the Haemonetics CLX bag which is no longer available. Plts will be stored in the Fenwal bag for as long as they could be stored in the Pall bag, and the storage time will be increased in 1-day increments until FDA acceptance criteria are not met.

- 1b) Determine the best PAS-to-plasma ratio for plt storage.

Using the optimum storage bag identified in Aim 1a and starting with a 65% PAS concentration at the maximum storage time identified above, the PAS concentration will be increased in 5% increments until FDA criteria are not met. If storage times cannot be improved, we will decrease the PAS concentration in 5% decrements from the 65% to determine if storage times can be increased. Continuing this iterative process of changing the PAS concentration and storage times will determine the maximum storage duration achievable and at what PAS concentration this occurred.

Specific Aim 2: Evaluate the effects of Mirasol treatment of autologous WB on extended storage of PAS-stored plt concentrates prepared from treated WB.

Subjects (#)	Timeline (Weeks)
20	8

Once we have optimized the storage conditions in Aim 1, we will Mirasol treat the WB, a plt concentrate will be prepared and stored using the optimum storage conditions. The storage time will be decreased by one-day intervals, if needed, to meet FDA acceptance criteria.

Specific Aim 3: Determine the post-transfusion recovery and survival of pre-storage pooled extended stored plt concentrates prepared from Mirasol-treated WB given to thrombocytopenic patients.

Patients (#)	Timeline (Weeks)
40	52

Four plt concentrates prepared as in Aim 2 (test plts) will be pre-storage pooled and added to Fenwal's 1000 ml PL2410 storage bag. After storage, a small aliquot of the pooled plts will be removed, radiolabeled, and transfused along with the remaining unlabeled plts into a thrombocytopenic patient. Post-transfusion plt recoveries and survivals will be determined by radioactivity as well as by plt counts to determine the comparability of plt viability results from these two methods. As a control, a small aliquot of plts obtained from a standard 5-day stored plt concentrate will be radiolabeled with another isotope and transfused concurrently with the test plts to determine the relative viability of the test and control plts. We will also document hemostatic efficacy and any adverse events associated with the pooled test transfusion.

Cold Apheresis Platelets in Isoplate (CAPI)

I. PROTOCOL INFORMATION

Title: Cold Apheresis Platelets in Isoplate (CAPI)

Phase of Study: Phase I/II. Proof of Principle.

Version/Date of Protocol: Version 3/July 27, 2016

II. SPONSOR INFORMATION

The study is being sponsored by the Department of Defense (DOD) Congressionally Directed Medical Research Program (CDMRP).

III. PRINCIPAL INVESTIGATOR'S INFORMATION

PI Name: Sherrill J. Slichter, MD

Title: Director Platelet Transfusion Research

Name & Address of Research Institution: BloodworksNW (formerly Puget Sound Blood Center)

Phone #: 206-689-6541

FAX #: 866-791-4098

Email: sherrills@BloodWorksNW.org

IV. ROLES AND RESPONSIBILITIES

Principal Investigator (PI): The PI will have overall responsibility for the study. She will ensure compliance with the protocol, institutional policies, and all applicable regulations. The PI will supervise the use of the test articles and review study data at regular intervals. The PI will permit and comply with audits and monitoring requirements. The PI will report all unanticipated problems involving risk to subjects or others to the Research Monitor, appropriate regulatory bodies, including the University of Washington Human Subjects Division and the USAMRMC, ORP, HRPO.

Study Coordinator (SC): The SC will assist in the preparation of the protocol, Institutional Review Board (IRB) applications and amendments, required quarterly reports, and other regulatory documents as needed. The SC will manage implementation of the research protocol under the supervision of the Principal Investigator. She will identify and recruit eligible subjects, review information on source documents to ensure data are complete and correct, and assist in rectifying discrepancies. She will maintain study records and logs and assist in evaluating study results. In addition the SC may perform all tasks ascribed to the Clinical Research Staff (below).

Clinical Research Staff (CRS) will perform research-related interventions under the direction of the PI and/or the SC. CRS will ensure that subjects have read and understand the informed consent document and have all questions appropriately answered and that informed consent documents are properly signed and dated. CRS will schedule study subject visits; explain study procedures; assess and document study subject's clinical status as required by research protocol; collect apheresis units; obtain subject blood samples; administer radiolabeled platelets as required by the protocol (only trained Registered Nurse CRS will perform this task); monitor study subject's progress and report adverse effects to the PI.

Laboratory Research Staff will add PAS and plasma to test and control units according to established procedure, perform research-related laboratory testing and platelet radiolabeling in accordance with

the study protocol. Laboratory Research Staff will perform data entry into the study data base. Upon occasion Laboratory Research Staff may also collect blood samples from subjects. BloodworksNW Staff (either research or non-research) will collect follow-up blood samples and hold them for pick up and processing by Laboratory Research Staff.

Research Monitor: The Research Monitor will act as the safety advocate for study subjects. The Research Monitor will review all unanticipated problems involving risk to subjects or others and will provide an unbiased written report of the event to appropriate regulatory bodies, including the University of Washington Human Subjects Division and the USAMRMC, ORP, HRPO.

V. SITE INFORMATION

All study activities with the exception of the laboratory tests noted below will occur at the BloodworksNW (formerly Puget Sound Blood Center) under the direction of Dr. Sherrill J. Slichter. Bacterial testing and Gram Staining will be conducted by the University of Washington (UW) Microbiology Laboratory in Seattle, or by LabCorp in Seattle. All samples sent to outside microbiology laboratories will be stripped of all personal identifiers and labeled with a study ID number only.

VI. STUDY INFORMATION

Type of Research: Biomedical

VII. STUDY DESIGN

Background

Platelets are transfused to prevent bleeding and induce hemostasis, and can thus be critical in saving lives following trauma and in supporting thrombocytopenic cancer patients. Currently, platelets collected from volunteers are stored at room temperature. Room temperature storage has been demonstrated to maximize platelet recovery and survival in transfused patients; however it also increases the opportunity for bacterial growth in the platelet unit. The FDA limits the shelf life of platelets to 5 days or less to minimize this bacterial risk. Recently, the FDA has allowed 7 day storage with additional point-of-release bacterial testing. Nonetheless, transfusion associated sepsis remains the principal lethal risk associated with platelet transfusion.

Cold storage (4°C) is known to reduce post transfusion platelet recoveries but the effect is no more than 10% to 20% after 3 days of platelet concentrate storage. However, survivals are reduced to 1 to 2 days compared to an average survival of 4 to 5 days at 22°C storage⁽¹⁻³⁾. In addition, there is controversy regarding the ability of 4°C stored platelets to correct bleeding times in thrombocytopenic patients compared to 22°C stored platelets⁽¹⁾. However, we have demonstrated, in preliminary studies that platelets stored within whole blood for 15 days have radiolabeled autologous recoveries of 27±11% (49% of the same donor's fresh autologous recoveries) and survivals averaging 1.2±0.4 days (16% of the same donor's fresh autologous survivals)⁽⁴⁾. These data suggest that 4°C storage of apheresis platelets, as proposed in this study, may clearly show similar or even better platelet viability as platelet storage within whole blood.

Platelet Additive Solution

Based on our preliminary studies using 22°C storage, apheresis platelets stored in a platelet additive solution allow the longest reported storage time of platelets⁽⁵⁾. Post transfusion platelet recovery and survival meet FDA guidelines for 13 days of storage. It is anticipated that storage at 4°C will also benefit by storage in an additive solution.

Cold Stored Platelets

While not conducive to maintaining circulating platelet counts in thrombocytopenic cancer patients, transfusion of refrigerated platelets for deployed military medical units might provide adequate platelet hemostatic capacity to bleeding trauma patients and improve platelet availability for such patients. Based on recent in vitro studies of 4°C versus 22°C stored platelets, clot strength, platelet aggregation and shear induced platelet aggregation are all better maintained at 4°C⁽⁶⁻⁸⁾. Furthermore, there is much less aggregation of platelets when the platelets are stored at 4°C in an additive solution and not agitated during storage. This possibility has been inadequately evaluated, particularly in clinical studies.

A deeper understanding of the effects of cold storage on platelet function could greatly aid in improving the availability of platelets on the battlefield and in the civilian transfusion setting. In this research proposal, we are interested in evaluating metabolic, functional and viability changes to apheresis platelets preserved in an additive solution and stored at 4°C. We will also determine the recovery and survival of these platelets by radiolabeling an aliquot of the apheresis platelets and re-infusing it into the donor/subject.

Current Research Approach

A double hyperconcentrated apheresis platelet unit will be collected from a healthy adult volunteer subject using the Trima Accel® Automated Blood Collection System. Concurrent plasma will also be collected. After collection the unit will be split into two equal portions. One half of the split unit will be re-suspended in either plasma or a combination of a platelet additive solution (PAS) and plasma. The ratio of PAS to plasma will be 65% PAS: 35% plasma. The other half of the split unit be suspended in plasma (without PAS) and will be stored, in the cold, for 3 days, which is the maximum platelet storage time allowed for refrigerated platelets by the FDA. The 3 day stored unit will serve as the control comparator. The plasma or PAS/plasma unit (test) will be stored for up to 20 days without agitation, at 4°C. Both units will achieve a final platelet concentration of $\sim 1500 \times 10^3$ platelets/ μ L.

On Day 3 the subject will receive an Indium 111 (In-111) radiolabeled aliquot of their control plasma 4°C stored platelets. Follow-up samples from the subject will be collected approximately 2 hours post-infusion and on Days 1 (2X), 2, 3, 4, and 5 to calculate recovery and survival of the subject's 3 day stored platelets. On Day 1 the sample draws will be 2 - 10 hours apart.

The plasma or PAS/plasma 4°C stored test platelets will initially be stored for 10 days. The subject will receive an infusion of In-111 aliquot of their plasma or PAS/plasma platelets. Follow-up samples, as above, will be collected to calculate platelet recovery and survival of the test unit.

These studies will allow comparison of the 3 and 10 day stored platelets. Indium will be used to label both control and test platelets because the other available isotope, chromium, is not taken up by refrigerated platelets. The In-111 administered on Day 3 will be largely undetectable by Day 10 and therefore re-use of the same isotope to measure both control and test cold stored platelets is valid. Additionally, we will collect a pre-infusion radioactivity sample to account for any residual In-111, and adjust our calculations accordingly.

Each subject's test platelet recovery and survival will be considered acceptable if they are $\leq 40\%$ less than the subject's corresponding 3-day stored sample measurements. Acceptance criteria are met for a given storage time if samples from all subjects in that group meet acceptability threshold.

So long as our acceptance criteria are met with 5 split paired units stored for 10 days we will progressively increase the storage period in two day increments until acceptance criteria are no longer met (i.e., when at least one subject has >40% reduction in either recovery or survival compared to the same subject's 3-day 4°C plasma stored platelets). We will evaluate 12, 14, 16, 18 and 20 day storage so long as test platelets for all 5 subjects in the group demonstrate ≤40% reduction in recovery and survival as compared to their own 3-day plasma 4°C stored platelets. Once we identify the first storage period that fails to meet acceptance criteria, we will fall back by one day to evaluate the mid storage period between that which met and that which failed criteria. If that mid-storage period fails, then we will evaluate the prior storage period again with 5 additional samples, continuing to step back down until a group meets acceptance criteria for all 10 subjects. Thus, once the maximum acceptable storage time has been determined, a total of 10 subjects satisfying acceptance criteria will have platelet viability data collected at that storage time.

In addition to radiolabeled platelet recovery and survival measurements, various in vitro assays (see "In Vitro Tests Performed on Test Units") will be performed at the end of each storage condition (3 day and extended stored; i.e. 10 to 20 day).

VIII. INCLUSION / EXCLUSION CRITERIA

Inclusion Criteria

The subject is in good health, is taking no excluded medications and meets platelet donor suitability requirements aimed at assuring donor safety. Recipient safety restrictions (e.g. travel and sexual contact) do not apply for this study. No infectious disease testing will be performed.

Specific inclusion criteria are:

- Weight: ≥125 pounds
- Hematocrit: ≥38%
- Platelet count ≥225X10³/mm³
- Temperature: ≤99.5°F
- Resting blood pressure: systolic ≤ 180 mmHg; diastolic ≤100 mmHg
- Resting heart rate: 40 to 100 beats per minute
- Subjects must be ≥ 18 years old, of either sex
- Subjects must be able to read, understand and sign the informed consent document and commit to the study follow-up schedule. The ability to read and speak English is required for participation.
- Subjects must have good veins for apheresis platelet collection and drawing blood samples.
- Subjects of child-bearing potential (either male or female) must agree to use an effective method of contraception during the course of the study. The following methods of contraception will be considered 'effective' when self-reported by subject; abstinence, intrauterine contraception devices, hormonal methods, barrier methods or history of sterilization.

Exclusion Criteria

Healthy subjects will be excluded from the study for any of the following reasons:

- Ever received radiation therapy.
- Already participated in 4 research studies involving radioisotopes within the contemporaneous calendar-year.

- Taken aspirin, non-steroidal anti-inflammatory, or other platelet affecting drugs within 72 hours of collection or infusion. Subjects who have ever been prescribed anti-platelet medications (e.g. clopidogrel) will be excluded from study participation regardless of the interval to their last dose.
- Currently pregnant or nursing as assessed during interview. A urine pregnancy test prior to radioisotope infusion is required for women of childbearing potential.
- Unable to comply with the protocol in the opinion of the investigator.
- Donated granulocytes within the last 2 days.
- Donated whole blood within the last 7 days.
- Donated platelets or plasma within the last 28 days.

IX. SUBJECT RECRUITMENT & SCREENING

The study will advertise for healthy adult volunteers on websites, newspapers and/or bulletin boards. Prospective subjects will be asked to contact the Study Coordinator by email or phone. Email inquiries will be answered, by the Study Coordinator, with a summary email along with attachments of study documents (study consent, HIPAA policy, directions to BloodworksNW and a schedule of study visits). The subject will be encouraged to call the Coordinator to discuss the study by phone before making a screening appointment. The Study Coordinator may reference *Talking Points for Volunteer Inquiries* during the phone conversation.

Prospective subjects responding by phone will speak with the Study Coordinator, as described above, and will be offered an email with attached study documents.

Individuals who wish to make an in person appointment for consent and screening will make those arrangements by phone or email with the Study Coordinator. An email confirmation and reminder will be sent by the Study Coordinator. Contact information from people who do not make appointments will not be retained.

A total of 80 subjects may be enrolled to achieve 40 complete data sets, which is the maximum number of evaluations our study design would demand.

X. INFORMED CONSENT PROCESS

At the time of the recruitment visit, Clinical Research Staff, usually the Study Coordinator will review the consent with the study subject in a private space at the BloodworksNW. The purpose of the study, the study procedures, the risks and options to not participate or to withdraw will be discussed. The number of venipunctures, the radioisotope exposure and the time demands of multiple blood draws will be emphasized. Throughout the process the subject will be encouraged to ask questions or make comments.

Subjects will sign the consent form in the presence of the staff administering the consent and that person will also sign the consent. The subject will be given a copy of the consent and HIPAA document.

After the subject has given informed consent eligibility screening will be performed. See Study Procedures section below. Screening questions are related to establishing that the subject is in good health. See Section 8, Inclusion/Exclusion Criteria.

All Clinical Research Staff have been trained and are certified in the Protection of Human Research Subjects.

XI. STUDY PROCEDURES

Screening

An abbreviated version of blood donor screening will be performed including completion of a study specific health history questionnaire, check of vital signs and a blood draw to obtain a 2 mL sample for a complete blood count (CBC) to obtain the hematocrit and platelet count. Only criteria aimed at assuring donor safety will apply. Recipient safety restrictions (e.g. travel and sexual contact) do not apply for this study. No infectious disease testing will be performed. If the subject meets eligibility criteria an appointment for apheresis platelet collection, within the next 35 days, will be made.

Apheresis Platelet Collection

Prior to apheresis the pre-apheresis health history questionnaire and check of vital signs will be repeated. The subject's platelets will be collected using the Trima Accel Automated Blood Collection System which is licensed by the FDA for this purpose. A venipuncture site will be selected and cleaned using standard BloodworksNW procedures. A needle will be placed in one of the subject's arms at the antecubital area. A CBC sample is obtained using an inline diversion pouch. Whole blood is drawn into the apheresis machine and the blood components are separated by centrifugation. Platelets and plasma are collected into storage bags and the red blood cells are returned to the subject. Along with the return of the subject's red blood cells the subject receives approximately 350 mL of ACD (citrate) anticoagulant during the collection process. The platelet apheresis collection lasts 2-3 hours. Subjects are observed throughout the collection by a nurse or technician specifically trained in apheresis.

Suspension in Additive Solution and Storage

Immediately after apheresis collection, using sterile technique, research laboratory staff will split the hyperconcentrated platelet unit into two equal portions and complete the processing and storage procedures. Half of the split unit will become the control comparator. The control unit will be suspended in plasma and stored for 3 days. The other half of the split will be the test unit. Test platelet units will be suspended in plasma only or a mixture of PAS and plasma at a 65%/35% ratio. Test units will be stored for ≥ 10 days. Both units will be placed in a refrigerator at $4 \pm 2^\circ\text{C}$. Neither the control nor test units will be agitated during storage. Both units will be stored in the Terumo ELP bag.

When PAS is utilized it will be added to half of the platelet collection to achieve the desired PAS to plasma ratio by weight. The product will rest at room temperature for approximately two hours. Serum total protein concentrations will be performed to ensure the desired concentration was achieved.

Platelet Additive Solutions are isotonic solutions used to replace a portion of the plasma to store leukocyte reduced apheresis platelets. Several of these solutions are FDA approved for storage in a 65% PAS/35% plasma mixture for up to 5 days at $20\text{--}24^\circ\text{C}$ with continuous agitation. Some FDA licensures associate the particular PAS with a specific collection devices or storage bag. None are approved for use with platelets stored in the cold. We will be using these storage solutions in an off-label manner as regards to the collection device and storage conditions. However, all of the collection devices and storage solutions are FDA approved for platelet collection and storage.

The control portion of the split unit will be suspended with plasma so that it equals the final weight of its paired test unit.

Temperature monitors will record temperatures and trigger alarms for out of range conditions. End of storage will be defined as the date and time when the aliquot for radiolabeling and infusion is removed from the stored unit.

Autologous infusion of radiolabeled platelets

Three days after the apheresis collection the subject will receive an infusion of radiolabeled platelets. The radiolabeled platelets administered on Day 3 will be extracted from the ½ split unit, suspended in plasma, and stored in a refrigerator at 4±2°C for 3 days and labeled with Indium 111.

Ten to 20 days after the apheresis collection the subject will receive another radiolabeled platelet infusion. An aliquot of platelets from the other ½ split unit, suspended in PAS and plasma, and stored in a refrigerator at 4±2°C for 10 to 20 days will also be labeled with Indium 111.

Prior to infusion the subject's health will be reassessed via interview. If the subject feels unwell, has flu-like symptoms, or has any significant negative change to his or her health status, then he/she will be considered ineligible for the radiolabeled infusion and will exit the study. Pre-menopausal female subjects will have a urine pregnancy test to confirm that they are not pregnant prior to both infusions. Any subject with a positive pregnancy test will be ineligible to continue with the infusion and will exit the study. Prior to infusion, microbiological tests (bacterial testing and Gram stain) of the platelet unit will be verified as negative.

Height and weight will be measured at the time of infusion. After venous access has been established, a blood sample (20 mL) will be obtained to determine baseline radioactivity. Approximately 10 mL (2-10 mL) of autologous radiolabeled platelets will be infused back into the subject. During each platelet infusion, the subject will be carefully monitored for adverse reactions; i.e., fever, chills, dyspnea, urticaria or pain (infusion site, chest pain or other). Any adverse reactions will be recorded and reported to the study investigator.

After infusion, the line will be flushed with saline and removed. The subject will remain at, or return to, BloodworksNW for the Day 0 post-infusion blood sample, which will be collected ≥2 hours after the infusion.

Follow-up

The subject will return to BloodworksNW for sample collection (10 mL of blood) for measurement of radioactivity to calculate platelet-survival curves; Day 1 (twice, 2-10 hours apart), Day 2, Day 3, Day 4, Day 5 for each radiolabeled platelet infusion. (See Schedule of Events below). These samples will be used to determine platelet recovery and survival using computerized modeling of a multiple hit decay function.

Schedule of Events

Study Day	Study Procedures
Day -35 to Day -1	Informed consent process Screening and enrollment
Day 0	 Apheresis platelet collection Apheresis unit split into two equal volumes in separate bags <ul style="list-style-type: none"> • ½ platelets suspended in plasma • ½ platelets suspended in selected PAS/plasma ratio Both platelet bags put into storage, unagitated, at 4±2°C
Day 1	Bacterial culture sample collected from both platelet units (4°C)
Day 3	3 day 4°C platelet storage ends. End of storage in vitro testing. Platelets processed for In-111 radiolabel Pre-infusion vital signs and health assessment 20 mL blood sample from subject for baseline radioactivity Infusion of In-111 radiolabeled platelets Post infusion R&S sample from subject (≥2 hours post infusion)
Day 4	Post infusion R&S sample from subject (twice, 2 - 10 hours apart)
Day 5	Post infusion R&S sample from subject
Day 6	Post infusion R&S sample from subject
Day 7	Post infusion R&S sample from subject
Day 8	Post infusion R&S sample from subject
Day 10 *	10 day 4°C platelet storage ends. End of storage in vitro testing. Platelets processed for 2 nd In-111 radiolabel. Pre-infusion vital signs and health assessment 20 mL blood sample from subject for baseline radioactivity Infusion of 2 nd aliquot of In-111 radiolabeled platelets Post infusion R&S sample from subject (≥2 hours post infusion)
Day 11	Post infusion R&S sample from subject (twice, 2 - 10 hours apart)
Day 12	Post infusion R&S sample from subject
Day 13	Post infusion R&S sample from subject
Day 14	Post infusion R&S sample from subject
Day 15	Post infusion R&S sample from subject Subject exits study

* The second In-111 labeling will be done at the end of storage for the test stored platelets which may be from 10 – 20 days after the apheresis collection.

Total Volume of Blood Collected

The total amount of blood loss during the course of the study is approximately 267 mL. This includes CBC (2 mL), diversion pouch sample (~25 mL), apheresis platelets (~60 mL residual in disposable kit), immediate pre-infusion for baseline radioactivity (20 mL X2), and post infusion blood samples (10 mL each X 14) to determine circulating radioactivity.

In addition to the above volumes, approximately 170 mL of apheresis platelets and up to 300 mL of concurrent plasma will be collected.

In Vitro Testing Schedule

In addition to the in vivo platelet viability measurements after re-infusion, a number of in vitro laboratory measurements will be performed. Samples for these experiments will be obtained from the apheresis unit at the end of storage for both the control and test units. These tests will be performed using standardized methods.

A sample from each platelet product will be sent for bacterial culture to an outside microbiology laboratory one day after the platelet collection. At the end of the storage period a sample from the stored platelet unit will be sent to the University of Washington Microbiology Lab for a Gram stain. If either test is positive, the subject's stored platelets will not be reinfused and the subject will be withdrawn from the study.

The following table provides a list of the tests that will be performed on the apheresis platelet unit at the beginning and end of storage. These are the standard in vitro assays that the FDA requires for platelet licensing.

In Vitro Tests Performed on Stored Apheresis Units at the End of Storage

Test Type	End of storage testing	
	Plasma suspended, 3 day stored unit.	PAS/plasma or plasma only suspended, 10 – 20 day stored unit
Platelet Concentration	✓	✓
Volume	✓	✓
Platelet yield	✓	✓
Blood Gases (pH and pCO ₂ , PO ₂ , HCO ₃)	✓	✓
Glucose and Lactate	✓	✓
P-selectin*	✓	✓
Morphology	✓	✓
Annexin V binding	✓	✓
Extent of Shape Change	✓	✓
Hypotonic Shock Response	✓	✓
Platelet Microparticles	✓	✓
Swirling	✓	✓
Mean Platelet Volume (MPV)	✓	✓
Bacterial Culture**	✓*	✓*
Gram stain	✓	✓

All samples will be discarded once testing is complete and no residual radiation is detectable.

*P-selectin samples will be prepped on end of storage day and batch tested.

**Bacterial Culture sample removed from unit 1 day after collection and evaluated at end of storage.

Adverse Event (AE) Assessments

During apheresis collection and infusion of platelets, the subject will be carefully monitored for adverse reactions; e.g., fever, chills, dyspnea, urticaria, or pain (infusion site, chest pain or other). Adverse reactions will be recorded in the study file and reported to the study investigator. Subjects will be instructed to report changes in health condition over the course of the study to the study coordinators. Minor AEs that are associated with venipuncture and blood collection, such as minor bruising at the needle site, will not be recorded as AEs, unless they worsen over time (e.g., become infected, etc.).

XII. DATA and ANALYSIS

Laboratory and other evaluable results will be transcribed from source documents (e.g. lab result print-outs) into an electronic database.

Summary statistics (means, medians, standard deviations, interquartile range) will be calculated for all in-vitro assays. A table of in vitro summary statistics will be presented to facilitate comparison of assay values between the 3 day and extended stored platelets from the same subjects.

Tables of recovery and survival summary statistics will display values by group from 3 day and extended stored platelets. Recovery and survival of extended stored platelets as percentage of corresponding 3-day 4°C stored platelets will be plotted against days stored. Regression methods will be used to determine if there is evidence of any trend in the mean storage or recovery as percentage of corresponding 3-day 4°C stored platelets with respect to storage time. Histograms of recovery and survival as percentage of corresponding 3-day 4°C stored platelet measurements will be plotted, and corresponding confidence intervals will be calculated. Counts and percentages of the number of subjects at each storage interval whose corresponding 3-day 4°C stored platelets have >20% loss will be tabulated to determine storage intervals for which the stored platelets meet performance criteria.

XII. LABELING & STORAGE OF DATA & SPECIMENS

Study records, samples, and test results will be identified with a unique identifier and access will be limited to sponsor authorized personnel, the investigator, site research staff, and authorized regulatory authorities, including representatives of the FDA.

An alpha-numeric code that is unique to this study will be used as study identifiers. The study ID number will be associated with the subject's name on a study ID log. That log and the study database will be kept in separate folders on an electronic network at BloodworksNW. BloodworksNW uses Active Directory NT Authentication along with Access Control Lists (ACL's) for all network folders. File and folder access is logged on network shares. Security is enforced by the Information Technology Department. A network firewall is used to prevent unauthorized access to the network from outside entities.

Source paper documents will be kept in the Study Coordinator's office at BloodworksNW which is a security-card-restricted-access-building. The door to the coordinator's office is kept locked. Any documents not needed for source documentation will be shredded using a secure records-destruction service.

The link between the subject's identify and their study data will be destroyed/deleted when the research ends and any required monitoring of the study is finished, which will be no later than December 31, 2025. Consents will be destroyed six years after the conclusion of data analysis.

BloodworksNW utilizes an independent waste management contractor to dispose of research samples. The waste management contractor is contractually obligated to be in compliance with all applicable regulations regarding the pick-up, transport and treatment of regulated medical waste.

Subject samples that are radioactive at the time of collection are stored on a secure-access floor until such time as they have no detectable residual radiation. This is generally about 2 weeks. At that point they are disposed of as described above.

XIII. RISK AND INJURY

Apheresis-Related Risks and Precautions

Risks associated with standard platelet-product apheresis procedures are listed below. A single apheresis procedure typically lasts about 3 hours.

- Venipuncture-related risks: Venipuncture may lead to apprehension, discomfort, pain, bruising or infiltration at the venipuncture site. A vasovagal response, such as lightheadedness or fainting, nausea, or vomiting may occur. There is a very small risk of infection at the venipuncture site.
- Citrate infusion related risks (hypocalcaemia): Citrate (Acid-Citrate-Dextrose) is added to the apheresis circuit as an anticoagulant. This may result in perioral tingling or paresthesias. Non-specific mild symptoms of hypocalcaemia include headaches, nervousness, irritability, lightheadedness, flushing, shivering, nausea, vomiting, chest discomfort and abdominal cramping. Slowing the collection rate, pausing the collection and/or administering oral calcium (TUMS) will effectively address these symptoms. Rarely, intravenous calcium is administered when symptoms do not resolve. If allowed to progress citrate toxicity could potentially manifest as muscle cramps, tremors, tetany, laryngospasm, seizures and life threatening cardiac arrhythmias.
- Blood Loss: In rare and unusual circumstances, blood loss has occurred due to inability to complete the procedure.

The following precautions will be taken: The subject's pre-apheresis vital signs (blood pressure, heart rate, temperature) and pre-apheresis hematocrit will be determined. Subjects will be visually monitored for signs of distress during all procedures by trained and experienced staff. Citrate reactions will be treated according to the standard treatments at the site, which includes oral or, rarely, intravenous calcium supplementation, and/or slowing, pausing or stopping the procedure.

Radioisotope Infusion-Related Risks and Precautions

The radiation dose in this study is less than annual background radiation (3 mSv) and is not known to be associated with any health hazard. The amount of the isotope that will be infused is ≤ 30 μ Ci of indium. The total radiation activity infused is ≤ 30 μ Ci. The total body effective dose is approximately 0.8 mSv. The total absorbed dose to the spleen is approximately 8.3 mGy. The risks of radiation exposure to a fetus are unknown. Therefore, women of childbearing potential will have a pregnancy test performed prior to the radiolabeled platelet infusion.

BloodworksNW's Platelet Transfusion Research Department will maintain a record of each subject's participation and will limit the number of studies any one individual can participate in to four studies in a calendar year. Patients who have received radiation therapy will be excluded from the study.

Platelet Transfusion-Related Risks and Precautions

Risks associated with receiving any blood product include chills, fever, hives, itching, immune response against blood cells, and/or blood infection from bacterial contamination. There is a rare risk of receiving the wrong subject's cells upon infusion, which could cause symptoms similar to those listed above.

The following precautions will be taken: In this study, subjects will be infused with their own cells; confirmation of identification will be done by two person verification of the infusion material. To prevent bacterial contamination, the product will be bacterially screened before infusion and sterile technique will be used for all manipulations of the study platelets.

Venipuncture-Related Risks and Precautions

Risks associated with venipuncture for blood sampling are apprehension, pain, discomfort, venospasm, fainting, bleeding, or bruising or infiltration at the venipuncture site.

The following precautions will be taken: Trained and experienced phlebotomists will perform the venipuncture procedures so that discomfort of the subject should be minimal.

XIV. BENEFIT(S)

There is no direct benefit to the study subject. Real benefits are altruistic in nature: subjects participating in this study will assist the scientific and medical communities in gathering important information to improving the availability of platelet transfusions.

XV. COMPENSATION

Subjects will receive \$1,000.00 at the conclusion of the study for their time involved in study participation. If the subject is unable to complete the entire study or has to be withdrawn from the study, they will receive partial payment for their time involved in the study. The partial payment scale is the following (number in parentheses equals the number of times each procedure occurs during the course of the study):

Initial screening (Day -35 to Day -1, one visit during this time period)	\$30
Apheresis collection (Day 0)	\$200
Infusion of radiolabeled platelets, including pre-infusion sample draw (Day 3 and Day 10 – 20. Two separate infusions)	\$100 (x2) = \$200
Follow-up blood sample, platelet recovery and survival calculation	\$35 (x14) = \$490
End of study exit	\$80
Total for completing all study procedures	\$1,000

XVI. CONFIDENTIALITY

BloodworksNW considers all data and information collected during this study confidential. All data used in the analysis and summary of this study will be anonymous, and without reference to specific subject names. Study records, samples, and test results will be identified with a unique identifier and access will be limited to sponsor authorized personnel, the investigator, site research staff, and authorized regulatory authorities, including representatives of the FDA.

XVII. USAMRMC REPORTING REQUIREMENTS FOR SAE

All unanticipated problems involving risk to subjects or others will be promptly reported by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the Human Research Protection Office (HRPO). A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army

Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

XX. LITERATURE REVIEW

1. Slichter SJ, Harker LA. Preparation and storage of platelet concentrates. II. Storage variables influencing platelet viability and function. *Br J Haematol* 1976;34(3):403-419.
2. Becker GA, Tuccelli M, Kunicki T, et al. Studies of platelet concentrates stored at 22C and 4C. *Transfusion* 1973;13, 61.
3. Murphy S, Gardner FH. Platelet preservation. Effect of storage temperature on maintenance of platelet viability – deleterious effect of refrigerated storage. *New England Journal of Medicine* 1969;280, 1094.
4. Slichter SJ, Fitzpatrick L, Jones MK, Pellham E, Bailey SL, Gettinger. In Vivo Viability of Platelets Stored in Whole Blood at 4°C. Submitted abstract, American Society of Hematology Annual Meeting; Orlando, FL December 5-8, 2015:184
5. Slichter SJ, Corson J, Jones MK, Christoffel T, Pellham E, Bailey SL, Bolgiano D. Exploratory studies of extended storage of apheresis platelets in a platelet additive solution (PAS). *Blood* 2014;123(2) 271-280.
6. Montgomery RK, Reddoch KM, Evani SJ, Cap AP, Ramasubramanian AK. Enhanced shear-induced platelet aggregation due to low-temperature storage. *Transfusion*. 2013 Jul;53(7):1520-30.
7. Nair PM, Pidcock HF, Cap AP, Ramasubramanian AK. Effect of cold storage on shear-induced platelet aggregation and clot strength. *J Trauma Acute Care Surg*. 2014 Sep;77(3 Suppl 2):S88-93.
8. Reddoch KM, Pidcock HF, Montgomery RK, Fedyk CG, Aden JK, Ramasubramanian AK, Cap AP. Hemostatic function of apheresis platelets stored at 4°C and 22°C. *Shock*. 2014 May;41 Suppl 1:54-61

Extended Storage of Pathogen-Reduced Platelet Concentrates (PRECON)

EDMS 5779/13335012

W81XWH-13-2-0089



PI: Sherrill J. Slichter MD

Org: Bloodworks Northwest

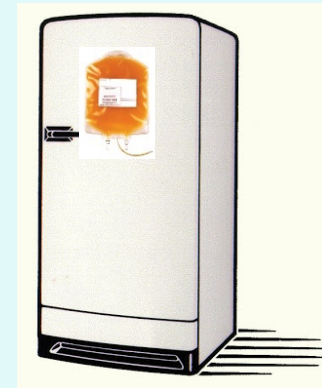
Award Amount: \$866,326

Study/Product Aim(s)

- Research related to cold storage of platelets derived from Whole Blood and Apheresis
- Storage of platelets in Platelet Additive Solution (PAS), currently Isoplate and Intersol vs. platelets stored in plasma

Approach

Study of apheresis platelets stored at 4°C in a platelet additive solution, or in plasma, entitled Cold Apheresis Platelets in Isoplate (CAPI). One half of the split unit will be stored in plasma at 4°C stored for 3 days (control), the other half will be stored in 65% PAS/35% plasma, or plasma without PAS, at 4°C for 10 - 20 days (test). Recovery and survival of $\leq 40\%$ less than the subject's corresponding 3-day stored sample measurements is acceptable.



Refrigerated platelets in PAS or plasma- stored for up to 20 days

Accomplishment: Enrollment ongoing to evaluate apheresis platelets at 4°C

Timeline and Cost

Activities	CY	14	15	16	17
Study evaluating platelets in WB at 4°C					
Development and regulatory approval of apheresis platelets in PAS at 4°C study					
IND for radiolabeling of platelets for autologous recovery and survival studies					
Apheresis platelets in PAS at 4°C study enrollment, data collection and analysis					
Estimated Budget (\$K)		\$142	\$220	\$577	\$866

Goals/Milestones

CY14 Milestones – Brrr Study ongoing enrollment

- ☒ Conduct of study evaluating platelets in WB at 4°C

CY15 Milestones – Completion of Brrr study and approvals for CAPI

- ☒ Completion of study evaluating platelets in WB at 4°C
- ☒ Submission for publication results of platelets in WB at 4°C

CY16 Goal – Regulatory approval and study initiation (CAPI)

- ☒ Final IRB approval
- ☒ HRPO approval
- ☒ Enrollment, data collection and analysis (in progress)

Comments/Challenges/Issues/Concerns

CAPI is an exploratory study only. For confirmation of results the FDA requires a full set of in vivo platelet recovery/survival data and complimentary in vitro platelet quality data for 22-24 subjects for the selected cold storage period.

Budget Expenditure to Date

Projected Expenditure: \$866,326

Actual Expenditure: \$577,888

Updated: 19-OCT-16